

## Prediction of malignancy in mediastinal lymph nodes during endobronchial ultrasound: A comparative validation study

*Endobronşiyal ultrasonografide lenf nodlarında malignite varlığının öngörülmesi: Karşılaştırmalı validasyon çalışması*

Nur Şafak Alici<sup>1</sup>, İbrahim Onur Alici<sup>2</sup>

<sup>1</sup>Department of Chest Diseases, Occupational and Occupational Diseases Polyclinic, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, İzmir, Türkiye

<sup>2</sup>Department of Chest Diseases, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, İzmir, Türkiye

### ABSTRACT

**Background:** In this study, we aimed to compare the diagnostic performances of three existing prediction tools in visually identifying a malignant lymph node.

**Methods:** Between April 2016 and January 2021, a total of 827 lymph nodes of 259 patients (211 males, 48 females; mean age: 61.1±7.2 years; range, 41 to 79 years) who underwent endobronchial ultrasound procedure for diagnosis and/or staging of lung cancer and diagnosis of mediastinal lymphadenopathy of unknown origin were retrospectively analyzed. This external validation study was designed to compare the diagnostic yields of the prediction tools developed by Shafiek et al., Alici et al., and Canada Lymph Node Score (CLNS). Endobronchial ultrasound-guided transbronchial needle aspiration results and predictions were compared to gold-standard tool.

**Results:** Overall, endobronchial ultrasound-guided transbronchial needle aspiration had a sensitivity, specificity, positive and negative predictive value, and accuracy of 95.6%, 100%, 100%, 97.6%, and 98.4%, respectively. Diagnostic performances of proposed tools were quite remarkable. Among them, Alici algorithm had a higher sensitivity and negative predictive value, which were matched by excellent specificity and positive predictive value offered by CLNS ≥3 and Shafiek tool. The area under the curve value of CLNS ≥3 was higher than Shafiek tool and CLNS ≥2.

**Conclusion:** Conventional prediction tools relying on simple real-time sonographic features were found to be consistent by the means of diagnostic performance in this external validation dataset. Despite being inferior to cytology, their superior performance was proven with defined individual strengths and weaknesses.

**Keywords:** Endobronchial ultrasound, lymphadenopathy, malignancy, prediction tool.

### ÖZ

**Amaç:** Bu çalışmada, malign lenf nodunun görsel olarak tespitinde mevcut üç öngördürücü aracın tanıtılma performansını karşılaştırıldı.

**Çalışma planı:** Nisan 2016 - Ocak 2021 tarihleri arasında akciğer kanserinin tanı ve/veya evrenmesi ve nedeni bilinmeyen mediastinal lenfadenopati tanısı için endobronşiyal ultrason işlemi yapılan 259 hastanın (211 erkek, 48 kadın; ort. yaş: 61.1±7.2 yıl; dağılım, 41-79 yıl) toplam 827 lenf nodu retrospektif olarak incelendi. Bu eksternal validasyon çalışması, Shafiek ve ark., Alici ve ark. tarafından geliştirilmiş ve Kanada Lenf Nodu Skoru öngördürücü (CLNS) araçlarının tanıtılma değerini karşılaştırmak üzere tasarlandı. Endobronşiyal ultrason kılavuzluğunda transbronşiyal iğne aspirasyon sonuçları ve öngördürmeleri altın standart yöntem ile karşılaştırıldı.

**Bulgular:** Genel olarak endobronşiyal ultrason kılavuzluğunda transbronşiyal iğne aspirasyonunun duyarlılığı, özgüllüğü, pozitif ve negatif prediktif değerleri ile doğruluk düzeyi sırasıyla %95.6, %100, %100, %97.6 ve %98.4 idi. Önerilen araçların tanıtılma performansı dikkat çekici düzeydeydi. Bunlar arasında Alici algoritması, CLNS ≥3 ve Shafiek aracı tarafından sunulan mükemmel özgüllük ve pozitif prediktif değeri ile eşleşen daha yüksek bir duyarlılığa ve negatif prediktif değere sahipti. CLNS ≥3'ün eğri altında kalan değeri, Shafiek aracı ve CLNS ≥2'den daha yüksekti.

**Sonuç:** Bu eksternal validasyon veri setinde tanıtılma performans araçları ile basit gerçek zamanlı sonografik özelliklere bağlı konvansiyonel öngördürücü araçlar tutarlı bulundu. Sitolojiden üstün olmasına da, üstün performans tanımlanan avantaj ve dezavantajları ile kanıtlandı.

**Anahtar sözcükler:** Endobronşiyal ultrasonografi, lenfadenopati, malignite, öngördürücü araçlar.

**Corresponding author:** Nur Şafak Alici.

E-mail: safak.alici@hotmail.com

Doi: 10.5606/tgkdc.dergisi.2023.22276

**Received:** June 03, 2021

**Accepted:** October 06, 2021

**Published online:** January 30, 2023

**Cite this article as:** Şafak Alici N, Alici İÖ. Prediction of malignancy in mediastinal lymph nodes during endobronchial ultrasound: A comparative validation study. Turk Gogus Kalp Dama 2023;31(1):63-68. doi: 10.5606/tgkdc.dergisi.2023.22276

©2023 All right reserved by the Turkish Society of Cardiovascular Surgery.



This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes (<http://creativecommons.org/licenses/by-nc/4.0/>).

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has become initial modality for mediastinal cytological staging of lung cancer.<sup>[1]</sup> During the procedure, an endosonographer gather real-time information on several sonographic features of a lymph node. A possible diagnostic utility of these features has been extensively studied. The very first study on this subject was reported by Fujiwara et al.<sup>[2]</sup> which showed promising results and encouraged several other investigators to publish their own analyses. Of those subsequent studies, three have offered practical prediction tools based on several sonographic features to discriminate malignant lymph nodes from benign ones.<sup>[3-5]</sup> They were remarkable, as they relied on relatively objective criteria, were quite simple to use in real-time situations and showed acceptable diagnostic performances. However, there are no studies giving a head-to-head comparison of their yield. In the present study, we aimed to compare the diagnostic performances of three existing prediction tools in visually identifying a malignant lymph node.

## PATIENTS AND METHODS

This single-center, retrospective validation study was conducted at Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, Department of Chest Diseases between April 2016 and January 2021. The diagnostic performances of three systems were compared in a single dataset. A total of 827 lymph nodes of 259 patients (211 males, 48 females; mean age: 61.1±7.2 years; range, 41 to 79 years) who underwent EBUS procedure for diagnosis and/or staging of lung cancer and diagnosis of mediastinal lymphadenopathy of unknown origin were included. All operations were performed by a single experienced endosonographer. Assessment of stations were done according to the International Association for the Study of Lung Cancer (IASLC) Lymph Node Map.<sup>[6]</sup> The data on the sonographic features were collected from reports of the procedures and existing video files. The visual and semi-quantitative system in a previous study was used to classify sonographic features.<sup>[3]</sup> Calculation and assignment of the scores to each lymph node was done retrospectively at the time of study with clear instructions of respective studies.<sup>[3-5]</sup>

The patients with benign diseases (sarcoidosis, tuberculosis, pneumoconiosis, etc.) and patients who received chemotherapy and/or radiotherapy were excluded as these conditions may alter the architecture and, thus, sonographic appearance of lymph nodes. Malignant lymph nodes diagnosed with EBUS-TBNA were assumed as true positives. All

negative results were confirmed with surgical biopsy or at least six months of progression-free follow-up. The EBUS-TBNA results and predictions by tools were compared to the gold standard (surgical results, true positive EBUS-TBNA results or six months of progression-free follow-up). Positive or surgically confirmed results between July 2020 and January 2021 were included, but negative results without surgical confirmation were excluded.

Endobronchial ultrasound and simultaneous transbronchial needle aspiration were performed under moderate-to-deep sedation with midazolam and remifentanyl in the operating room. A convex probe EBUS (BF-UC180F, Olympus, Tokyo, Japan) was used to examine the lymph nodes, and the ultrasound images were processed with a dedicated scanner (EU-ME1, Olympus, Tokyo, Japan).

## Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) for continuous variables and in number and frequency for categorical variables. Three systems were compared with receiver operating characteristics (ROC) curve analysis. The diagnostic performances of three prediction tools in

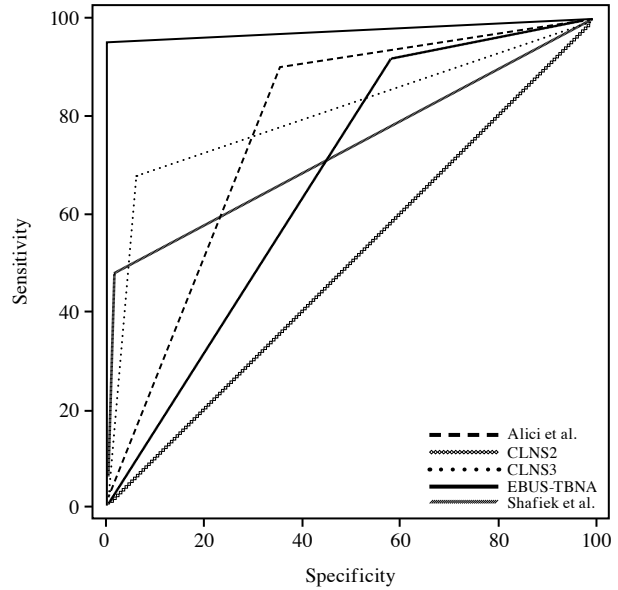
**Table 1. Characteristics of lymph nodes and primary condition**

	n	%
Lymph node stations (n=827)		
7	215	26.0
4R	197	23.8
11R	146	17.7
4L	118	14.3
11L	101	12.2
10R	22	2.7
2R	12	1.5
10L	9	1.0
Others	7	0.8
Diagnosis of primary condition (n=259)		
Adenocarcinoma	95	36.7
Epidermoid carcinoma	92	35.5
Small cell cancer	31	12.0
Other lung cancer subtypes	8	3.1
Benign lymphoid hyperplasia	33	12.7

**Table 2. Sonographic features of lymph nodes and percent of positive scores**

Sonographic features	All LN (n=827)			Malignant LN (n=295)			Benign LN (n=532)			p		
	n	%	Mean±SD	Min-Max	n	%	Mean±SD	Min-Max	n		%	Mean±SD
Size												
Size ≥10 (mm)	555	67.1	14.4±11.0	3.9-56.2	253	85.7	18.9±10.1	4.1-56.2	302	56.7	12.0±10.8	3.9-36.0
Hypoechoic	814	98.4			294	99.7			520	97.7		
Heterogenous	313	37.8			181	61.4			132	24.8		
Round	387	46.8			251	85.1			136	25.6		
Distinct margin	764	92.4			285	96.6			479	90.0		
Presence of necrosis	16	1.9			9	3.1			7	1.3		
Presence of calcification	28	3.4			7	2.4			21	3.9		
Absence of central hilar structure	281	34.0			224	75.9			57	10.7		
Positive results of prediction tools (in AO)												
Alici algorithm	455	55.0			266	90.2			189	35.5		
CLNS ≥2	585	70.7			272	92.2			313	58.8		
CLNS ≥3	234	28.3			200	67.8			34	6.4		
Shafiek tool	153	18.5			142	48.1			11	2.1		

LN: Lymph node; SD: Standard deviation; AO: Alpha betical order; CLNS: Canada Lymph Node Score; \* Independent samples t-test; \*\* Chi-squared test.



**Figure 1.** Comparative receiver operating characteristics (ROC) curves.

comparison with EBUS-TBNA cytological yield by the means of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios, area under curve (AUC) and accuracy were given. A *p* value of <0.05 was considered statistically significant with 95% confidence interval (CI).

## RESULTS

Of a total of 827 lymph nodes, 178 (21.5%) were surgically confirmed. The prevalence of malignant disease was 295/827 (35.6%). Main characteristics of the involved lymph nodes are given in Table 1. The most common lymph nodes were subcarinal, paratracheal, and interlobar lymph nodes. The most common malignancy was adenocarcinoma, followed by epidermoid carcinoma. Benign lymphoid hyperplasia constituted 12.7% of all cases.

Sonographic features of the lymph nodes are given in Table 2. Malignant nodes were larger, more hypoechoic, and more heterogeneous. They were mostly round and had distinct margins. The presence of calcification and necrosis was similar between malignant and benign lymph nodes. The absence of central hilar structure was mostly seen in malignant lymph nodes.

In these patients, EBUS-TBNA had a sensitivity, specificity, PPV, and NPV, and accuracy of 95.6%, 100%, 100%, 97.6% and 98.4%, respectively.

**Table 3. Comparison of the diagnostic performances of scoring systems**

	Sensitivity (95% CI)		Specificity (95% CI)		+LR	-LR	PPV	NPV	AUC (95% CI)		Accuracy	<i>p</i>
EBUS-TBNA	95.6	92.6-97.6	100.0	99.3-100.0	-	0.04	100.0	97.6	0.978	0.965-0.987	98.4	<b>&lt;0.001</b>
Alici algorithm	90.2	86.2-93.3	64.5	60.2-68.5	2.54	0.15	58.5	92.2	0.773	0.743-0.801	73.6	<b>&lt;0.001</b>
CLNS $\geq$ 2	92.2	88.5-95.0	41.2	36.9-45.5	1.57	0.19	46.5	90.5	0.667	0.634-0.699	59.3	<b>&lt;0.001</b>
CLNS $\geq$ 3	67.8	62.1-73.1	93.6	91.2-95.5	10.61	0.34	85.4	83.9	0.807	0.778-0.833	84.4	<b>&lt;0.001</b>
Shafiek tool	48.1	42.3-54.0	97.9	96.3-99.0	23.28	0.53	92.8	77.3	0.730	0.699-0.760	80.1	<b>&lt;0.001</b>

CI: Confidence interval; LR: Likelihood ratio; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under curve; EBUS-TBNA: Endobronchial ultrasound guided transbronchial needle aspiration; CLNS: Canada lymph node score.

**Table 4. Statistical significance of head-to-head comparisons**

	EBUS-TBNA	Alici algorithm	CLNS $\geq$ 2	CLNS $\geq$ 3	Shafiek tool
EBUS-TBNA		<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Alici algorithm	<b>&lt;0.001</b>		<b>&lt;0.001</b>	0.083	0.062
CLNS $\geq$ 2	<b>&lt;0.001</b>	<b>&lt;0.001</b>		<b>&lt;0.001</b>	<b>0.013</b>
CLNS $\geq$ 3	<b>&lt;0.001</b>	0.083	<b>&lt;0.001</b>		<b>&lt;0.001</b>
Shafiek tool	<b>&lt;0.001</b>	0.062	<b>0.013</b>	<b>&lt;0.001</b>	

EBUS-TBNA: Endobronchial ultrasound guided transbronchial needle aspiration; CLNS: Canada lymph node score; Statistically significant results were written in bold character.

The AUC value for malignant disease was 0.978 (95% CI: 0.965-0.987;  $p=0.0001$ ). Diagnostic performances of proposed prediction tools were quite good despite being significantly lower than cytology (Figure 1, Tables 3 and 4). Compared to each other, all tools performed well. Among them, the Alici algorithm had a higher sensitivity and NPV, which were matched by excellent specificity and PPV offered by Canadian Lymph Node Score (CLNS)  $\geq$ 3 and the Shafiek tool. The AUC value of CLNS  $\geq$ 3 was higher than the Shafiek tool and CLNS  $\geq$ 2.

## DISCUSSION

Accurately defining nodal involvement is crucial in lung cancer staging. Traditionally, clinicians rely on cytological and/or histopathological specimens for this purpose regarding inconsistent results given by computed tomography (CT) and positron emission tomography (PET).<sup>[7,8]</sup> Endobronchial ultrasound-guided transbronchial needle aspiration is the main instrument for this purpose. Beyond localizing the node in the mediastinum for an accurate sampling, ultrasound images give very important data on the architecture of the node. Sonographic characteristics may guide an endosonographer to select the node to be or not to be sampled and also give additional information, when there is a discordance

between clinical staging and cytologic results.<sup>[3,9]</sup> There are several studies on the sonographic features of a metastatic lymph node. Among them, three research groups have offered practical prediction tools to find affected lymph nodes.

The first tool was published by Shafiek et al.<sup>[5]</sup> in 2014. They used two discrete datasets to challenge and validate the tool. One of the main strengths of this study was the presence of two raters to decide on the sonographic features. The authors initially focused on six criteria (round shape, distinct borders, heterogeneous echogenicity, absence of visible central hilar structure, size of  $\geq$ 10 mm, and presence of hyperechogenic density). Primary analysis revealed the non-significant effect of presence of a hyperechogenic density in the interior of a lymph node. Therefore, they modified the criteria which was partly borrowed from Schmid-Bindert et al.<sup>[10]</sup> and performed a validation in the second arm. Variable multiplier factors were defined for size, shape, margin, echogenicity, and absence of central hilar structure. The computed result was analyzed with the ROC curve and modified tool with a score of  $>5$  showed a sensitivity of 78% and specificity of 86% in the detection of a malignant nodes (AUC=0.852; 95% CI: 0.743-0.928;  $p=0.0001$ ).

Second tool by Alici et al.<sup>[3]</sup> was developed with decision tree analysis, thus, formed as an algorithm.

In the beginning, they randomly divided the cases into two groups: experimental arm and study arm. The algorithm was developed in the experimental arm and validated in the study group. The findings in the second arm resulted in a modification of the algorithm in its final form. They reported the sensitivity, specificity, NPV, and PPV, and accuracy of the algorithm as 100%, 51.2%, 50.6%, 100%, and 67.5%, respectively. When its high sensitivity and PPV were considered, they concluded that the tool might be useful in choosing true positive nodes in a particular nodal station rather than indicating an unnecessary sampling. The study attracted attention with its detailed visual classification atlas based on Fujiwara's original criteria.<sup>[2]</sup> The atlas clearly defines the sonographic features with corresponding images. Despite offering a useful tool which can be used during real-time EBUS procedures, the study failed to give a proper interrater variability which was clearly mentioned as a prominent limitation of the study.

Hylton and et al.<sup>[9]</sup> have been studying prediction tools for years. After a systematic review on this subject, they reported an easy-to-use and reliable prediction tool, the CLNS, recently.<sup>[4]</sup> They conducted the study in two parts. The first part was data collection and assessment of validity. In this part, data on sonographic features were collected prospectively according to Fujiwara's criteria<sup>[2]</sup> and video files were obtained by a screen-recording device. They developed the predictive tool with logistic regression analyses on those data with taking account of  $\beta$ -coefficients. In the second part, those video files were re-evaluated by a Canada-wide pre-educated rater team. The tool showed a cut-off value of  $\geq 2$  in the study population, but they decided to increase the cut-off value to  $\geq 3$  regarding the probability of malignant disease in comparative groups. The CLNS (cut-off  $\geq 3$ ) had given a sensitivity, specificity, PPV, and NPV of 31.5%, 96.3%, 65.4%, and 86.5%, respectively. With its high specificity and NPV, the tool seems to be useful in finding true negatives which may not be sampled during EBUS procedure. The methodology of the study is also remarkable with unmatched data on inter-rater variability. As an easy-to-use tool, the inter-rater reliability of a CLNS  $\geq 3$  was very good:  $0.81 \pm 0.02$  (95% CI: 0.77-0.85).

There were other prediction tools by Schmid-Bindert et al.,<sup>[10]</sup> which served as a basis for the study by Shafiek et al.,<sup>[5]</sup> and by Evison et al.<sup>[11]</sup> as one of the first studies on this issue. We did not involve those tools in the comparative validation analyses for some reasons. First, Schmid-Bindert et al.<sup>[10]</sup> involved benign diseases

in their study (sarcoidosis 10% and tuberculosis 10%). These diseases may alter the architecture of the lymph node with enlargement, clarification of the borders, heterogeneous texture (particularly in case of tuberculosis), necrosis, calcification, and deformation of the hilum. The data based on such lymph nodes would be erroneous. Pre-selection of cases is of particular importance as the results heavily depend on those. This was the case in CLNS study, Hylton et al.<sup>[4]</sup> excluded the cases who received neoadjuvant chemotherapy to avoid a potential confounding factor. In their study, Shafiek et al.<sup>[5]</sup> did not give detailed inclusion/exclusion criteria, but it seems reasonable that they did not involve a patient who received such treatments as they reported that the patients underwent EBUS procedure for lung cancer staging and investigation of suspected malignancy.<sup>[5]</sup> However, there were no detailed data on the composition of non-malignant group. Therefore, the external validation dataset in this study is of particular importance, as we only included malignant nodes and reactive hyperplasia. Other benign diseases such as sarcoidosis may act as a confounding factor and result in underestimation of diagnostic performance of the tools. Another reason not to involve Schmid-Bindert tool was that the proposed criteria was already shared by Shafiek et al.<sup>[5]</sup> with a minimal modification.

Another tool by Evison et al.<sup>[11]</sup> was developed to make a risk stratification model for negative results by EBUS. The authors aimed to guide the multidisciplinary teams while deciding which patients with a negative result by EBUS needed further staging procedures. They involved the findings in CT and PET to weigh the risk of false negative results. Endosonographers mostly have information on CT and/or PET findings of the patient before EBUS procedure and these findings may guide them while performing the procedure. However, these are complex scores and could not be compared directly with simple predictive tools involved in this study.

In this head-to-head comparison, all tools failed to rival cytological analysis. Still, there is no score to substitute cytological analyses. All three tools (Alici, CLNS  $\geq 3$  and Shafiek) were accurate. The AUC values were statistically not different between Alici and CLNS  $\geq 3$ ; the AUC of Shafiek tool was slightly lower than CLNS  $\geq 3$ . All were useful, however, not in the same way. The Alici algorithm still overestimates the possibility of malignant nodes, but may be useful in deciding the node to be sampled. The CLNS  $\geq 3$  and Shafiek tools have an excellent specificity to be

used in deciding not to sample. The CLNS  $\geq 2$  offers a good sensitivity to point out malignant nodes; however, it cannot find true benign nodes. Its superiority in sensitivity is attenuated by the lowest specificity and accuracy. Of them, the simplest tools are CLNS and Alici which can be easily used during real-time EBUS procedure.

This study is remarkable with its high lymph node number and methodology which offers a head-to-head comparison of existing prediction tools. However, there are also several limitations to the study. First, it is a retrospective analysis. A prospective validation should be carried out in the future. Second, the procedures were done by a single endosonographer and a proper inter-rater variability could not be reported. Finally, the data did not give information on a possible place of non-conventional sonographic analyses such as vascular pattern or elastography. In conclusion, conventional prediction tools relying on simple real-time sonographic features were found to be consistent by means of diagnostic performance in this validation dataset. Despite individual strengths and weaknesses, their superior performance was clearly proven. However, they did not offer the desired diagnostic yield to be used instead of cytology. Different characteristics shall be studied and implied to serve as a basis to a probable future's "digital sampling".

**Ethics Committee Approval:** The study protocol was approved by the Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Local Ethics Committee (date: 12.01.2021, no: 8). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from each patient.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** All authors contributed equally to the article.

**Conflict of Interest:** The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

**Funding:** The authors received no financial support for the research and/or authorship of this article.

## REFERENCES

1. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143(5 Suppl):e211S-e250S. doi: 10.1378/chest.12-2355
2. Fujiwara T, Yasufuku K, Nakajima T, Chiyo M, Yoshida S, Suzuki M, et al. The utility of sonographic features during endobronchial ultrasound-guided transbronchial needle aspiration for lymph node staging in patients with lung cancer: A standard endobronchial ultrasound image classification system. *Chest* 2010;138:641-7. doi: 10.1378/chest.09-2006
3. Alici IO, Yilmaz Demirci N, Yilmaz A, Karakaya J, Özyayın E. The sonographic features of malignant mediastinal lymph nodes and a proposal for an algorithmic approach for sampling during endobronchial ultrasound. *Clin Respir J* 2016;10:606-13. doi: 10.1111/crj.12267
4. Hylton DA, Turner S, Kidane B, Spicer J, Xie F, Farrokhyar F, et al. The Canada Lymph Node Score for prediction of malignancy in mediastinal lymph nodes during endobronchial ultrasound. *J Thorac Cardiovasc Surg* 2020;159:2499-507.e3. doi: 10.1016/j.jtcvs.2019.10.205
5. Shafiek H, Fiorentino F, Peralta AD, Serra E, Esteban B, Martinez R, et al. Real-time prediction of mediastinal lymph node malignancy by endobronchial ultrasound. *Arch Bronconeumol* 2014;50:228-34. doi: 10.1016/j.arbres.2013.12.002
6. El-Sherief AH, Lau CT, Wu CC, Drake RL, Abbott GF, Rice TW. International Association for the Study of Lung Cancer (IASLC) lymph node map: Radiologic review with CT illustration. *Radiographics* 2014;34:1680-91. doi: 10.1148/rg.346130097
7. Muehling B, Wehrmann C, Oberhuber A, Schelzig H, Barth T, Orend KH. Comparison of clinical and surgical-pathological staging in IIIA non-small cell lung cancer patients. *Ann Surg Oncol* 2012;19:89-93. doi: 10.1245/s10434-011-1895-9
8. Cetinkaya E, Turna A, Yildiz P, Dodurgali R, Bedirhan MA, Gürses A, et al. Comparison of clinical and surgical-pathologic staging of the patients with non-small cell lung carcinoma. *Eur J Cardiothorac Surg* 2002;22:1000-5. doi: 10.1016/S1010-7940(02)00581-X
9. Hylton DA, Turner J, Shargall Y, Finley C, Agzarian J, Yasufuku K, et al. Ultrasonographic characteristics of lymph nodes as predictors of malignancy during endobronchial ultrasound (EBUS): A systematic review. *Lung Cancer* 2018;126:97-105. doi: 10.1016/j.lungcan.2018.10.020
10. Schmid-Bindert G, Jiang H, Kähler G, Saur J, Henzler T, Wang H, et al. Predicting malignancy in mediastinal lymph nodes by endobronchial ultrasound: A new ultrasound scoring system. *Respirology* 2012;17:1190-8. doi: 10.1111/j.1440-1843.2012.02223.x
11. Evison M, Morris J, Martin J, Shah R, Barber PV, Booton R, et al. Nodal staging in lung cancer: A risk stratification model for lymph nodes classified as negative by EBUS-TBNA. *J Thorac Oncol* 2015;10:126-33. doi: 10.1097/JTO.0000000000000348